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KLARQUIST SPARKMAN, LLP
Suite 1600
One World Trade Center
121 SW Salmon Street
Portland, OR 97204-2988

EXAMINER	
DUNSTON, JENNIFER ANN	
ART UNIT	PAPER NUMBER
1636	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/26/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/692,553	COURT ET AL.	
	Examiner	Art Unit	
	Jennifer Dunston	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *8/23/2006, 8/28/2006, 12/8/2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-13,22 and 23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-13,22 and 23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *23 August 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This action is in response to the amendment, filed 8/23/2006. Applicant's arguments have been thoroughly reviewed, but are not persuasive for the reasons that follow. Any rejections and objections not reiterated in this action have been withdrawn. **This action is FINAL.**

Response to Amendment – 37 CFR 1.121(c)

The amendment to the claims filed on 8/23/2006 does not comply with the requirements of 37 CFR 1.121(c) because the proper status identifier was not provided for claim 1. Claim 1 is indicated as (original); however, the claim was amended. Claim 1 should have been provided with the status identifier (currently amended). Amendments to the claims filed on or after July 30, 2003 must comply with 37 CFR 1.121(c) which states:

(c) *Claims*. Amendments to a claim must be made by rewriting the entire claim with all changes (*e.g.*, additions and deletions) as indicated in this subsection, except when the claim is being canceled. Each amendment document that includes a change to an existing claim, cancellation of an existing claim or addition of a new claim, must include a complete listing of all claims ever presented, including the text of all pending and withdrawn claims, in the application. The claim listing, including the text of the claims, in the amendment document will serve to replace all prior versions of the claims, in the application. In the claim listing, the status of every claim must be indicated after its claim number by using one of the following identifiers in a parenthetical expression: (Original), (Currently amended), (Canceled), (Withdrawn), (Previously presented), (New), and (Not entered).

(1) *Claim listing.* All of the claims presented in a claim listing shall be presented in ascending numerical order. Consecutive claims having the same status of "canceled" or "not entered" may be aggregated into one statement (*e.g.*, Claims 1–5 (canceled)). The claim listing shall commence on a separate sheet of the amendment document and the sheet(s) that contain the text of any part of the claims shall not contain any other part of the amendment.

(2) *When claim text with markings is required.* All claims being currently amended in an amendment paper shall be presented in the claim listing, indicate a status of "currently amended," and be submitted with markings to indicate the changes that have been made relative to the immediate prior version of the claims. The text of any added subject matter

must be shown by underlining the added text. The text of any deleted matter must be shown by strike-through except that double brackets placed before and after the deleted characters may be used to show deletion of five or fewer consecutive characters. The text of any deleted subject matter must be shown by being placed within double brackets if strike-through cannot be easily perceived. Only claims having the status of "currently amended," or "withdrawn" if also being amended, shall include markings. If a withdrawn claim is currently amended, its status in the claim listing may be identified as "withdrawn—currently amended."

(3) *When claim text in clean version is required.* The text of all pending claims not being currently amended shall be presented in the claim listing in clean version, *i.e.*, without any markings in the presentation of text. The presentation of a clean version of any claim having the status of "original," "withdrawn" or "previously presented" will constitute an assertion that it has not been changed relative to the immediate prior version, except to omit markings that may have been present in the immediate prior version of the claims of the status of "withdrawn" or "previously presented." Any claim added by amendment must be indicated with the status of "new" and presented in clean version, *i.e.*, without any underlining.

(4) *When claim text shall not be presented; canceling a claim.*

(i) No claim text shall be presented for any claim in the claim listing with the status of "canceled" or "not entered."

(ii) Cancellation of a claim shall be effected by an instruction to cancel a particular claim number. Identifying the status of a claim in the claim listing as "canceled" will constitute an instruction to cancel the claim.

(5) *Reinstatement of previously canceled claim.* A claim which was previously canceled may be reinstated only by adding the claim as a "new" claim with a new claim number.

The nature of the non-compliance did not preclude an examination of the elected invention on the merits, the results of which are presented below in the interest of compact prosecution.

Receipt is acknowledged of the amendment filed 8/23/2006, in which claims 2 and 14-21 were canceled, and claims 1, 3-7, 12 and 22 were amended. Currently, claims 1, 3-13, 22 and 23 are pending.

Election/Restrictions

Applicant elected of Group I without traverse in the reply filed on 12/5/2005. Currently, claims 1, 3-13, 22 and 23 are under consideration.

Priority

Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosures of the prior-filed applications, International Application No. PCT/US01/25507 and Provisional Application Nos. 60/225,164 and 60/271,632, fail to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. The prior-filed application numbers do not provide literal or inherent support for the claimed method steps of claims 1-13 and 22. While the prior-filed applications suggest that the disclosed method of homologous recombination may be used to construct complex conditional targeting vectors, the specifications do not set forth the claimed method steps. For example, the prior-filed applications do not provide adequate written description for the method step of using homologous recombination to insert a nucleic acid encoding a selectable marker flanked by a pair of second recombining sites and a first recombining site into a second site into the gene in a bacterial artificial chromosome. The prior-

filed applications do not teach how to use the disclosed recombination system to make a vector for the conditional knockout of a gene, where two first recombining sites remain in a gene and recombination of the two first sites produces a nucleic acid sequence that cannot be transcribed to produce a functional protein.

Claims 1-13 and 22-23 have an effective filing date of 2/12/2003.

Specification

The disclosure is objected to because of the following informalities: the deposit numbers have not been provided for the deposited nucleotide cassettes (see page 44). Appropriate correction is required.

This objection was made in the Office action mailed 2/22/2006 and is reiterated above, because deposit numbers have not been provided for the blanks found at lines 28 and 29 of page 44. Applicant must replace all blanks within the specification with deposit numbers where appropriate.

Response to Amendment – 35 U.S.C. § 1.131

The declarations filed on 8/23/2006 (signed by Daiguan Yu, Pentao Liu, Donald Court and E-Chiang Lee), 8/28/2006 (signed by Neal Copeland and Nancy Jenkins), and 12/8/2006 (signed by Hilary Ellis) under 37 CFR 1.131 have been considered but is ineffective to overcome the Cassanova et al reference applied under 35 USC §§ 102(a) and 103(a).

The evidence submitted is insufficient to establish a reduction to practice of the invention in this country or a NAFTA or WTO member country prior to the effective date of the

Cassanova et al reference (Genesis, Vol. 32, No. 2, pages 158-160, published online 2/13/2002). The declaration and attached exhibits have been fully reviewed. The declaration attempts to provide evidence of an actual reduction to practice prior to the effective date of the Cassanova et al reference. Upon careful review, it has been determined that the declaration does not provide evidence that the claimed method had been reduced to practice prior to 2/13/2002. The declaration does not provide evidence that a nucleic acid encoding a selectable marker flanked by a second pair of recombining sites and a first recombining site was used for homologous recombination. The vectors of the declaration appear to contain only a pair of LoxP sites flanking a selectable marker. These LoxP sites correspond to the selectable marker flanked by a pair of first recombining sites and the selectable marker flanked by a second pair of recombining sites; however they lack the required first recombining site in combination with the second recombining sites, which is required by claim 1. Accordingly, the declaration does not provide evidence that a nucleic acid encoding a selectable marker flanked by a second pair of recombining sites and a first recombining site was made and used in the claimed invention prior to the effective date of the Cassanova et al reference. Accordingly, the declaration is insufficient.

Response to Arguments - 35 USC § 102

The rejection of claims 1, 3, 4 and 13 under 35 U.S.C. 102(a) as being anticipated by Casanova et al (Genesis, Vol. 32, No. 2, pages 158-160, Published Online 2/13/2002) has been withdrawn in view of Applicant's amendment to the claims in the reply filed 8/23/2006.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 3-10, 12, 13, 22 and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Casanova et al (Genesis, Vol. 32, No. 2, pages 158-160, Published Online 2/13/2002; see the entire reference) in view of Lee et al (Genomics, Vol. 73, pages 56-65, 2001; see the entire reference) as evidenced by Buchholz et al (Nucleic Acids Research, Vol. 24, pages 3118-3119, 1996; see the entire reference). This rejection was made in the Office action mailed 2/22/2006 and has been altered to address the cancellation of claim 2 in the reply filed 8/23/2006.

Casanova et al teach a method for generating a vector for conditional knockout of a gene, comprising the following steps: (i) co-electroporating a BAC construct and a kanamycin cassette flanked by two LoxP sites (LoxP-Kan-LoxP) into *E. coli* JC8679 competent cells, (ii) selecting for kanamycin resistant clones, (iii) transforming the BAC DNA, from a bacterial colony that had undergone homologous recombination, into Cre-expressing bacteria to excise the nucleic acid encoding the selectable marker, which leaves a single LoxP site in the gene (iv) co-electroporating into *E. coli* JC8679 competent cells the BAC DNA comprising the single LoxP site and a plasmid comprising a FRT-PGK$_{Tn5}$neo-FRT-loxP flanked by two homology arms, and (v) transforming the resulting recombinant BAC into FLP-expressing bacteria to excise the marker gene (e.g. page 158, left column, 2nd full paragraph; page 158, paragraph bridging

columns; Figure 1). Casanova et al teach the use of ET-cloning (homologous recombination in *E. coli* to insert the nucleic acid molecules encoding a selectable marker into the BAC construct (e.g. Figure 1). Casanova et al teach that the recombination of the remaining two first recombining sites will produce a nucleic acid sequence that cannot be transcribed to produce a functional protein (e.g. page 158, left column, 2nd paragraph). Casanova et al teach the abovementioned method, where the first recombining sites comprise a LoxP site, and the second recombining sites comprise a FRT site. Casanova et al teach the use of markers that confer resistance of the cell to an antibiotic such as kanamycin (e.g. Figure 1). Further, Casanova et al teach the use of Cre-expressing and Flp-expressing bacteria as taught by Bucholz et al (1996).

Bucholz et al is cited merely to provide evidence that the Cre-expressing bacteria used by Casanova et al comprise an inducible pL promoter operably linked to a nucleic acid encoding the Cre recombinase (e.g. page 3118).

Casanova et al do not teach homologous recombination wherein the cell comprises the pL promoter operably linked to a nuclei acid encoding Beta, Exo and Gam and wherein the first recombination site is FRT and the second recombination site is LoxP. Further, Casanova et al do not teach the use of Flpe recombinase encoded by a nucleic acid comprising an inducible promoter operably linked to a nucleic acid encoding the recombinase.

Lee et al teach a PL operon encoding beta, exo and gam under the control of the temperature-sensitive λ repressor (allele cI857) for use in BAC engineering (e.g. page 56, right column, 1st full paragraph; page 57, left column, 1st full paragraph). Further, Lee et al teach the use of the recombination system in combination with the flpe gene under the control of the P_{BAD} inducible promoter (e.g. strain EL250; Table 1). Lee et al teach that the recombination system is

highly efficient and can produce recombination frequencies that are at least 50- to 100-fold higher than those obtained with plasmid based systems (e.g. page 64, left column, last paragraph). Lee et al teach the recombination of an FRT-kan-FRT cassette into the mouse *Eno2* gene within a BAC vector (e.g. page 57, *Construction of plasmids*; Figure 1). Lee et al teach that the use of flpe provides a higher recombination frequency than the original flp gene (e.g. page 60, left column, 1st paragraph). With regard to the use of the recombination system for the construction of conditional targeting vectors, Lee et al state the following:

> This recombination system also facilitates the generation of complicated conditional targeting vectors. While the generation of such vectors often used to take several months, it can now be performed in only a few weeks. The ability to express reversibly Cre or Flpe recombinases in *E. coli* speeds this process even further. A selectable marker flanked with *loxP* of *FRT* sites can now be introduced into an intron of a gene and then be removed by transient Cre of Flpe expression, leaving behind a solo *loxP* or *FRT* site in the intron. See page 64, right column, 2nd paragraph.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method for generating a vector for conditional knockout of a gene of Casanova et al to include the phage lambda recombination system and inducible flpe expression taught by Lee et al because Casanova et al and Lee et al teach it is within the ordinary skill in the art to use homologous recombination in *E. coli* to engineer BAC vectors to produce conditional targeting constructs. Further, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method to use FRT sites as the first recombination site and LoxP as the second recombination site because Casanova et al teach it is within the ordinary skill in the art to use of a LoxP-Kan-LoxP cassette to insert a single LoxP site and Lee et al teach it is within the ordinary skill of the art to use a FRT-Kan-FRT cassette to insert an

FRT site into the intron of a gene. Further, Lee et al teach that the LoxP and FRT sites can be used interchangeably.

One would have been motivated to make such a modification in order to receive the expected benefit of increased efficiency of homologous recombination and FRT site-specific recombination, which would decrease the amount of time required to make the targeting construct, as taught by Lee et al. Further, one would have been motivated to use FRT in place of LoxP and LoxP in place of FRT to have more options in the vector design and subsequent knockout of the gene by expressing cre or flpe in a targeted mouse, for example. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Claims 1, 3, 4, 6-8, 10-13, 22 and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Casanova et al (Genesis, Vol. 32, No. 2, pages 158-160, Published Online 2/13/2002; see the entire reference) in view of Stewart et al (US Patent No. 6,355,412; see the entire reference) as evidenced by Buchholz et al (Nucleic Acids Research, Vol. 24, pages 3118-3119, 1996; see the entire reference). This rejection was made in the Office action mailed 2/22/2006 and has been altered to address the cancellation of claim 2 in the reply filed 8/23/2006.

The teachings of Casanova et al are described above and applied as before. Further, Casanova et al teach the use of Cre-expressing and Flp-expressing bacteria as taught by Bucholz et al (1996).

Bucholz et al is cited merely to provide evidence that the Cre-expressing bacteria used by Casanova et al comprise an inducible pL promoter operably linked to a nucleic acid encoding the Cre recombinase (e.g. page 3118).

Casanova et al do not teach homologous recombination wherein the cell comprises the pL promoter operably linked to a nuclei acid encoding Beta, Exo and Gam and wherein the cell is a eukaryotic cell.

Stewart et al teach a method of performing homologous recombination in a host cell, comprising introducing a nucleic acid sequence encoding RecE/T or Redα/β recombinase (i.e. Lambda Exo and Beta) into a host cell, introducing a polynucleotide comprising a nucleotide sequence homologous to the nucleotide sequence of interest into the host cell, activating the expression of RecE/T, and selecting a cell from the population in which homologous recombination has occurred (e.g. column 28, lines 10-50; column 29, lines 9-35; column 28, line 51 to column 29, line 8; columns 25-27; paragraph bridging columns 37-38). Further, Stewart et al teach the use of Gam in addition to Exo and Beta or RecE/T (e.g. column 25, lines 5-28; Example 1). Stewart et al teach that a variety of host-vector systems may be utilized to introduce and express the protein-coding sequence of RecE/T or Redα/β, including prokaryotic and eukaryotic cells such as bacterial, yeast, plant, rodent, mice, human, insect or mammalian cells (e.g. column 28, lines 10-40). With respect to regulatory controls, Stewart et al teach that a range of different expression levels and a variety of regulatory sequences are known in the art and the ability to generate a wide range of expression is advantageous for utilizing the method (e.g. column 25, lines 5-44; column 24, line 50 to column 25, line 3). Stewart et al teach that the expression can be regulated by the P_L promoter of phage λ and the inducible lambda repressor

CI_{857} (e.g. column 26, lines 1-27). Stewart et al teach that the nucleotide sequence of interest may be extrachromosomal and located on a bacterial artificial chromosome (e.g. column 20, lines 37-57; paragraph bridging columns 28-29). Moreover, Stewart et al teach that the lambda recombinases can be used to achieve high-efficiency targeted cloning (e.g. column 11, lines 3-47).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method for generating a vector for conditional knockout of a gene of Casanova et al to include the lambda beta, exo and gam genes operably linked to the pL promoter as taught by Stewart et al because Casanova et al and Stewart et al teach it is within the ordinary skill in the art to use homologous recombination to modify BAC constructs in a cell.

One would have been motivated to make such a modification in order to receive the expected benefit of being able to conduct high efficiency recombination in a variety of host cell types as taught by Stewart et al. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Response to Arguments - 35 USC § 103

With respect to the rejection of claims 1, 3-10, 12, 13, 22 and 23 under 35 U.S.C. 103(a) as being unpatentable over Casanova et al in view of Lee et al, as evidenced by Buchholz et al, Applicant's arguments filed 8/23/2006 have been fully considered but they are not persuasive.

The response essentially asserts that the Cassanova et al publication is removed as a reference by the declaration under 37 C.F.R. § 1.131, and the other references of record do not

teach or suggest the claimed invention. This is not found persuasive, because the declaration does not provide sufficient evidence to demonstrate an actual reduction to practice prior to the date of the Cassanova et al reference for the reasons set forth above in response to the declaration under 37 C.F.R. § 1.131.

For these reasons, and the reasons made of record in the previous office actions, the rejection is maintained.

With respect to the rejection of claims 1, 3, 4, 6-8, 10-13, 22 and 23 under 35 U.S.C. 103(a) as being unpatentable over Casanova et al in view of Stewart et al, as evidenced by Buchholz et al, Applicant's arguments filed 8/23/2006 have been fully considered but they are not persuasive.

The response essentially asserts that the Cassanova et al publication is removed as a reference by the declaration under 37 C.F.R. § 1.131, and the other references of record do not teach or suggest the claimed invention. This is not found persuasive, because the declaration does not provide sufficient evidence to demonstrate an actual reduction to practice prior to the date of the Cassanova et al reference for the reasons set forth above in response to the declaration under 37 C.F.R. § 1.131.

For these reasons, and the reasons made of record in the previous office actions, the rejection is maintained.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Dunston whose telephone number is 571-272-2916. The examiner can normally be reached on M-F, 9 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Jennifer Dunston, Ph.D.
Examiner
Art Unit 1636

jad

CELINE QIAN, PH.D.
PRIMARY EXAMINER